VERTEBRAL OSTEOPOROSIS

FOLLOWING

ACUTE SPINAL CORD INJURY

Dissertation submitted to the Dr. M.G.R.Medical University, Chennai, in practical fulfilment of the requirements for the M.D.in Physical Medicine and Rehabilitation, May 2011

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Certificate

This is to certify that this thesis entitled **"Vertebral osteoporosis following acute spinal cord injury"** is the bona fide work of Dr. Jacob George and was conducted at the Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore.

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Certificate

This is to certify that this thesis entitled **"Vertebral osteoporosis following acute spinal cord injury"** is the bona fide work of Dr. Jacob George and was conducted at the Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore, under the direct supervision and guidance of

Guide

Dr. George Tharion

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Contents

List of abbreviations

SCI	Spinal Cord Injury
BMD	Bone mineral density
QCT	Quantitative computed tomography
DEXA	Dual energy x-ray absorptiometry

INTRODUCTION

INTRODUCTION

Spinal cord injury (SCI) is a traumatic insult to the spinal cord that can result in alteration of normal motor, sensory and autonomic function. It is one of the most catastrophic injuries because of its multi-system involvement. Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Persons with SCI experience musculoskeletal effects of non-weight bearing throughout their lives. Osteoporosis is one of the complications of SCI.

Considerable magnitude of bone mass lost in the lower limbs following acute SCI (1, 2). Prospective studies suggest individuals with SCI can lose up to 40% of their bone mass at lower limb sites in the acute post-injury stages (3, 4, 5). The decline in bone density has been detected as early as 6 weeks post SCI and has been shown to steadily progress over the next 12 to 16 weeks before stabilizing. The fracture prevalence in the SCI population has been reported to be as great as 70% (6).

Comprehensive care and early rehabilitation has improved the quality of life of people following SCI. However osteoporosis among this group of individuals often predisposes them to risk of secondary fractures and related complications.

Osteoporosis is now widely recognised as a public health problem since this disease, which increases bone fragility and thereby the risk of fractures, is associated with high mortality, morbidity and medical expenses throughout the world (7).

The bone mineral density (BMD) can be measured by Quantitative computerised tomography (QCT).QCT allows for a three dimensional true density measurements of bone without super imposition of other tissues and therefore provides exact three dimensional anatomic localisation of the measured tissue (8). Bone density can be calculated separately in trabecular and cortical bone compartments. It makes possible a direct measurement of density (gm/cm^3) at any vertebral site. Selective measurement of high turnover trabecular bone, such as the central portion of the vertebral body, is of some advantage because it excludes cortical bone and extra osseous calcification.

JUSTIFICATION OF THE STUDY

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The majority of the patients who come for rehabilitation under Physical Medicine and Rehabilitation here have spinal cord injury. The development of osteoporosis among these patients is a concern as in addition to paralysis they have, they are immobilised initially for 2 to 3 months. The secondary osteoporosis that develops in these patients often predisposes them to the risk of secondary fractures and related complications. Radiological studies suggest that approximately one third of bone mineral lost within 3-4 months of SCI, after which time the loss slows down. The osteoporosis that accompanies SCI patients predisposes them to fracture after minor trauma, and the estimated incidence of fracture after SCI is 5 to 20 %. Fractures in persons with SCI are clinically relevant; they predispose to exuberant callus that may cause pressure sores or may mimic infection or thrombosis. Fractures are often complicated by profuse diaphoresis and increase in spasticity. In view of the importance of trying to prevent this common complication in the SCI population it was decided to quantify the incidence of osteoporosis in them during initial immobilisation period.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Introduction

Osteoporosis and associated fractures increase markedly with age and are a major cause of mortality and morbidity-and thus of medical expense- throughout world. The combined total risk for fracture due to osteoporosis is about 35%. Osteoporosis is a disease that occurs commonly in the rehabilitation patient population in its primary and secondary forms (9). Osteoporosis is a well recognised complication of SCI and radiological studies suggest that approximately one third bone mineral is lost within 3-4 months of SCI, after which time the loss slows. Osteoporosis is a disease of the skeletal system characterised by low bone mass and deterioration of bone tissue leading to an increased risk of bone fractures (7, 10, 11). Persons with traumatic SCI undergo transition immediately from a normal ambulatory life style to a state of markedly impaired mobility. Bone mineral loss occurs throughout the entire skeleton, except the skull (10).

Conceptual Definition of Osteoporosis

Various definition of osteoporosis have been offered to describe the outcome of events (fragility fractures), the process giving rise to porous bones, or the resultant diminution in bone mass. The following definition is now generally accepted “a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk” (7, 13).

Operational Definition of Osteoporosis

The relationship between BMD and fracture risk is continuous, and an estimate of BMD therefore provides an effective assessment of fracture risk. It is thus possible to choose a value for BMD that defines the presence of osteoporosis.

Bone mineral content or density (BMC or BMD) in young healthy women (peak bone mass) is normally distributed, irrespective of the measurement technique used. By virtue of this normal distribution, BMD values in individuals may be expressed in relation to a reference population in standard deviation (SD) units; this reduces the problems associated with calibration differences between instruments. Use of SD units in relation to the young healthy population is referred to as the t-score, where the mean is ascribed a value of zero.

The World Health Organisation has proposed two diagnostic thresholds of BMD for Caucasian women, based on the distribution of skeletal mass in young healthy individuals; these thresholds permit the establishment of four general diagnostic categories (14).

1. Normal: A value for bone mineral within 1 SD of the young adult reference mean. (t-score $\geq$ - 1.0)
2. Low bone mass (osteopenia) : A value for bone mineral more than 1 SD below the young adult mean but less than 2.5 SD below this value. (t-score -1.1 to - 2..5)
3. Osteoporosis: A value for bone mineral 2.5 SD or more below the young adult mean. (t-score $\geq$ - 2.5)
4. Severe (established) osteoporosis: A value for bone mineral 2.5 SD or more below the young adult mean in the presence of one or more fragility fractures.

Suitable diagnostic cut-off values for non-caucasian women and for men are less secure. It has been suggested that a similar absolute value for BMD to that used in women can be taken as a cut-off point for the diagnosis of osteoporosis in mean- that is, a value 2.5 SD below the average for adult pre menopausal women. It should be recognised that cut-off values are arbitrary and may differ according to sites measured, age and type of equipment.

Thus, the decrease in bone mass with changes in micro-architecture and consequent increased fragility represents the disease, whereas low-energy fractures represent a complication of the disease that will occur when the force applied to a bone, such as that resulting from falling, exceeds its load-bearing capacity (7). Thus, the osteoporotic fracture depends upon several internal and external factors that are not directly related to the osteoporotic process.

Classification of Osteoporosis (9)

Osteoporosis can be classified according to localisation in the skeleton and aetiology. Localised osteoporosis affects part of the skeleton; generalised osteoporosis affects, to a greater or lesser extent, different parts of the whole skeleton. Both types of osteoporosis can further be classified into primary and secondary osteoporosis.

1. Primary Osteoporosis: basic aetiology unknown, no associated disease
    a. Postmenopausal : elderly women
    b. Senile osteoporosis: elderly men
2. Secondary Osteoporosis: secondary to inherited or acquired abnormalities/diseases
    a. Hyperparathyroidism
    b. Cushing's disease
    c. Multiple myeloma
    d. Hyperthyroidism (endogenous and iatrogenic)

e. Idiopathic hypercalciuria
    i. Due to renal calcium leak
    ii. Due to renal phosphate leak
f. Malabsorption (including partial gastrectomy)
g. 25-OH vitamin D deficiency
    i. Due to chronic liver disease
    ii. Due to chronic anticonvulsant therapy (phenytoin, barbiturates)
h. 1,25-OH vitamin D deficiency
    i. Due to chronic renal failure
i. Adult hypophosphatemia
j. Osteogenesis imperfecta tarda
k. Male hypogonadism (Klinefelter's syndrome)
l. Female hypogonadism (Turner's syndrome)
m. Conditions consistent with hypoestrogenism secondary to anorexia and/or exercise
    i. Anorexia nervosa
    ii. Exercise induced amenorrhoea
n. Condition associated with disuse
    i. Paraplegia/hemiplegia
    ii. Immobilisation
    iii. Prolonged bed rest
o. Alcoholism
p. Diabetes Mellitus
q. Rheumatoid arthritis
r. Chronic obstructive pulmonary disease

s. Systemic mastocytosis

t. Condition associated with the use of medications

    i. Corticosteroids

    ii. Heparin

    iii. Anticonvulsants

    iv. Excess thyroid hormone

u. Malignancy

Aetiology and risk factors

Osteoporosis fracture risk is dependent on an individual's peak bone mass and strength of bone achieved in one's life time and the subsequent rate of bone loss. Multiple etiologic factors may act independently or in combination in an individual patient to produce diminished bone mass.

Risk factors for fractures (9)

Personal history of low-impact fractures

Current low bone mineral density

History of fracture in a first degree relative

Caucasian race

Advanced age

Female sex

Dementia

Recurrent falls

Inadequate physical activity

Poor health/ frailty

Current smoker

Low body weight

Oestrogen deficiency

Corticosteroid use

Testosterone deficiency

Vitamin D deficiency

Low life time calcium intake

Alcoholism

Impaired eye sight despite correction

Pathogenesis (15)

The pathogenesis of osteoporosis is complex in childhood and adolescent period; rate of bone formation exceeds resorption, resulting in continued skeletal growth and denser, longer and heavier bones. This process slows down in adulthood and peak bone mass is attained at about 30 years of age. After this, resorption begins to exceed formation. Normal bone loss averages 0.7% per year. It gets accelerated at the time of menopause to 2-5 % per year, which may continue for up to 10 years. Since cancellous bone loss is metabolically much more active than cortical bone, in periods of accelerated bone loss cancellous bone loss is three fold greater. Osteoporotic fractures therefore commonly occur in vertebrae.

Peak bone mass is primarily determined by genes but may be modified to a considerable extent by factors such as physical activity, calcium, vitamin d nutrition, smoking, alcohol, concurrent illness and medications- glucocorticoids and antiepileptics. The level of peak bone mass achieved at puberty is a major determinant of bone mass in later life and hence an important factor in the ultimate development of osteoporosis.

Cellular abnormalities

Conclusive evidence of cellular abnormalities contributing to the pathogenesis of osteoporosis is lacking. It may be that failure of osteoblast (the cell responsible for bone formation), due to either decreased cell number or decreased cell activity, may accompany advancing age but is not specific for osteoporosis (9).

Diagnosis

The first clinical indication of osteoporosis, either primary or secondary, will usually be a fracture. An absolute diagnosis of osteoporosis is usually made when an atraumatic fracture occurs in the presence of low bone mass (most typically of the spine, femur, and/or distal radius). However it is obviously of value from the standpoint of patient management to evaluate the patient at risk for the fracture before a fracture occurs, as well as to determine the cause of the fracture in patients in whom a fracture has occurred. Because the amount of bone mass present is the principal determinant of fracture, a non-invasive technique for quantifying bone mass would consequently be of value not only in the diagnosis of osteoporosis, but also in following a response to therapy.

Methods for measuring bone mass

Bone mass measurements and biochemical markers of bone turnover are key methods to diagnose osteoporosis, predict future fracture, and monitor therapeutic regimens.

Biochemical markers of bone turnover

Markers of bone formation

Serum

- Osteocalcin
- Bone specific alkaline phosphatase

Markers of bone resorption

Plasma

- Tartrate-resistant acid phosphatise
- Free pyridinoline and deoxy pyridinoline and type I collagen N and C- telopeptides breakdown products

Urine

- Urinary pyridinoline and deoxypyridinoline (collagen cross links) and type I collagen N and C – telopeptides breakdown products
- Fasting urinary calcium and hydroxyproline
- Urinary hydroxylysine glycosides

Roberts et al (16) demonstrated a dramatic rise in bone resorption markers, beginning within the first week of injury and peaking around weeks 10 to 16. Depending on the resorption marker examined, the peak was as high as 10 times the upper limit of normal.

Values had not returned to baseline at 6 months, indicating ongoing loss of bone. Contrasting with large rise in resorption markers, the change in markers of bone formation was modest and barely exceeded the reference range.

Quantification of bone mass

Most commonly used techniques

1. Single and dual photon absorptiometry (SPA and DPA respectively)
2. Quantitative computed tomography
3. Single or dual energy x-ray absorptiometry
4. Peripheral quantitative computed tomography
5. Ultra sound

Attenuation or absorption of ionising radiation by bone is the basic principle used in the majority of the noninvasive techniques (with the exception of ultrasound). A generally linear relationship exists between bone mass and radiation attenuation: the greater the amount of bone present, the greater the attenuation of ionising radiation, and subsequently the less radiation quantitated in a detector (9).

DXA is the clinical 'gold standard' for diagnosing osteoporosis (17). DXA allows the measurement of bone mineral density in the axial and peripheral skeleton. Bone density measurements can be obtained within 30 seconds to 2 minutes with a radiation exposure of approximately 10 m rad (one-sixth the exposure of a chest x-ray) with 99% precision and approximately 97% accuracy (9). However, the DXA technology for diagnosing osteoporosis by measuring bone density became available in India only in 1997 (15).

Quantitative computed tomography (QCT)

QCT allows for a three-dimensional true density measurement of bone without superimposition of other tissues and therefore provides exact three-dimensional anatomic localisation of the measured tissue (18). Bone density can be calculated separately in trabecular and cortical bone compartments. QCT is widely available now as a standard clinical examination of the bone density of the lumbar spine. Selective measurement of high turnover trabecular bone, such as the central portion of the vertebral body, is of some advantage because it excludes cortical bone and extra osseous calcification.

Single energy QCT is usually applied for routine examinations. A low dose, low energy exposure resulting in an effective dose of typically 50 uSv (including lateral digital radiograph) with essentially no gonad exposure. Dual energy QCT can improve accuracy, but technical considerations and a higher radiation dose limit this technique's use to research applications.

QCT not only provides information on BMD, but also on bone structure for the regions examined. QCT results are expressed as mgm of K_2HPO (dipotassium hydrogen orthophosphate) per cubic cm of bone volume, reflecting a true three dimensional density rather than the two dimensional area of DXA.

Interpretation of BMD analysis report

The measurements, which are carried out to three decimal places are given in mg per cubic cm. They are used to determine the T score and the Z score. The T score assesses the risk of fracture. It compares the subject's BMD with the predicted mean peak BMD (in an average 30 year old of the same sex) and expresses the difference in standard deviation (SD). In other words, the T score shows how the subject's BMD compares with ideal level.

A patient who's BMD is 1SD below that of an average 30 year old has a T score of -1. The Z score determines whether the subject's bone loss is out of proportion with what is expected. It compares the subject with the mean for age matched, sex matched and ethnic matched controls and express the difference in SD. Thus a 70 year old woman with a Z score of -1 is 1 SD below the BMD of the average 70 year old woman, but her T score is -3 because she is 3 SD below the BMD of the average 30 year old woman. The T score is useful in assessing a patient's risk of fracture and deciding whether to recommend pharmacological therapy. In general, almost all patients whose BMD is in the osteoporotic range should be considered for such therapy. Many patients with values in the osteopenic range, particularly those in the lower end of the range or with several risk factors for fracture, should also be considered for pharmacological therapy.

In a meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures, Marshal et al concluded that BMD can identify people who are at increased risk of developing a fracture, but it cannot with any certainty identify individuals who will develop a future fracture (19). It was also found that most measuring sites (proximal radius, distal radius, hip, lumbar spine, calcaneus and all sites) had virtually the same predictive ability for a decrease of 1 SD in bone density.

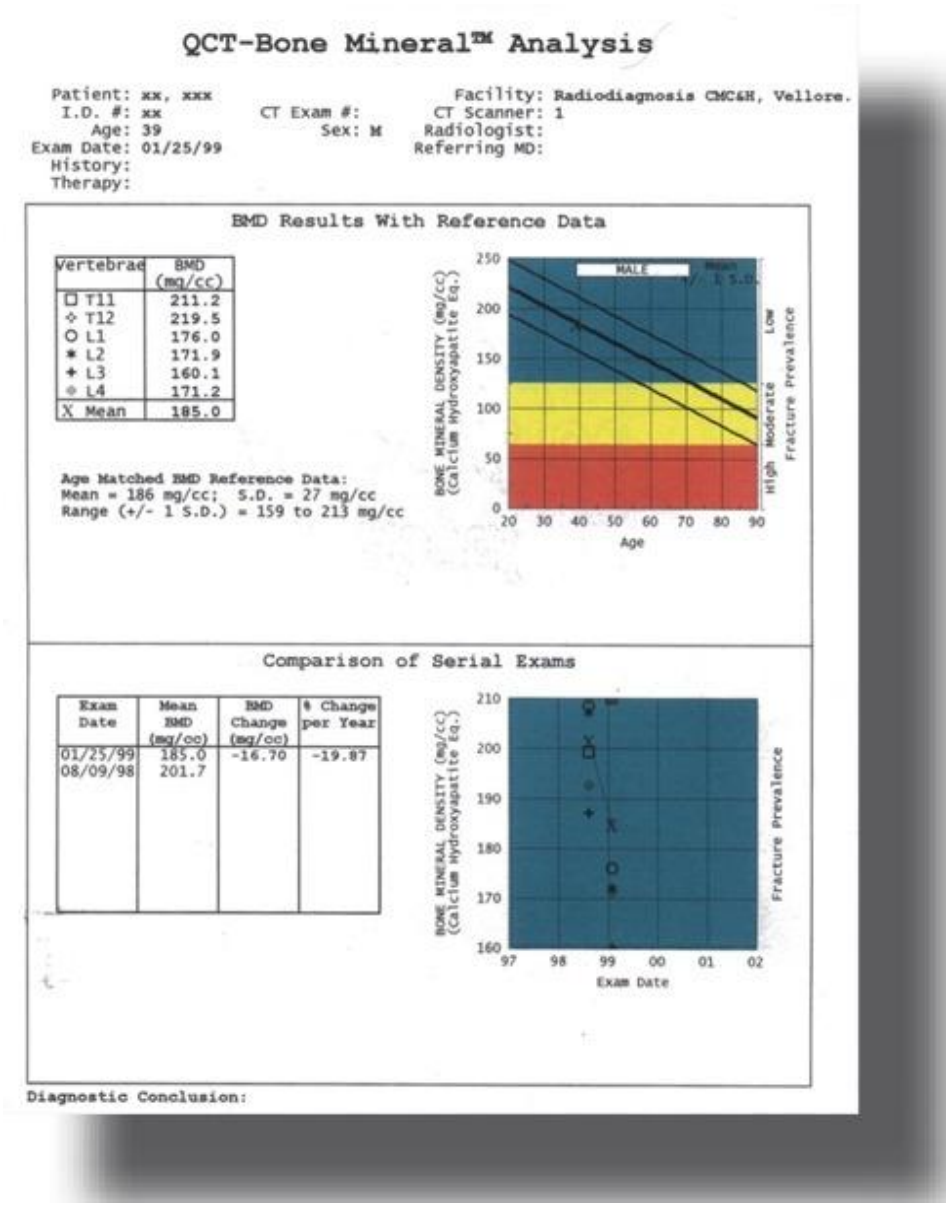

Figure 1: QCT - BMD report

Management of Osteoporosis

Because osteoporosis results in fractures due to minimal trauma, rapidly effective therapy is required to reduce fracture (20).Treatment of osteoporosis includes pharmacological and non-pharmacological methods.

Non-Pharmacological treatment

The avoidance of lifestyles known to result in bone loss, including cigarette smoking, excessive alcohol intake, lack of exercise, and so forth, should be addressed along with recommendations for nutritional and pharmacologic therapy (9). Morse et al reported that increased alcohol consumption after SCI may exacerbate sub-lesion bone loss (21).

Fall prevention

A multifactorial approach that addresses vision deficits, balance and gait abnormalities, cognitive impairment and dizziness is the cornerstone of fall prevention. Improving lighting, removing loose rugs and adding grab bars near bathtubs, toilets and stairways can enhance safety (22).

Nutritional adjuncts

Calcium

It is a mainstay of osteoporosis prevention and treatment. Recommended minimum calcium intake is 1000 to 1500 mg/day in all peri menoupausal and post menoupausal women and for men is 800 mg to 1500 mg. Calcium is generally safe (in the absence of a history of previous kidney stones, or of idiopathic hypercalciuria), comparatively inexpensive and logistically simple to ingest. A predisposition for kidney stones and nephrolithiasis may be seen.

A urinary calcium excretion of up to 250 mg per 24 hours is acceptable in individual without a history of kidney stones (9).

Vitamin D

400 to 800 IU per day of vitamin D is recommended. This will help to increase calcium absorption at the gut level, and use of active form of vitamin D analog as calcitriol may result in increased risk for kidney stones or for hypercalciuria, nephrolitiasis, or even nephrocalcinosis (9).

Protein

Along with calcium and vitamin D supplementation, it has been shown favourable outcomes in patients who have sustained hip fractures. RDA for protein is 44 g/day for women and 56 g/day for men (9).

Pharmacological treatment

The treatment of osteoporosis and osteopenia is directed at preservation or improvement of bone mass at the specific target sites. Because bone mass is the principal, although not the only, determinant of fracture, such preservation or improvement of bone mass is associated with a reduced risk of fracture. The axial and appendicular sites exhibit varying proportions of cortical (compact) and trabecular (cancellous) bone. Trabecular bone is metabolically more active than cortical bone (9). Trabecular bone appears to be preferentially altered in osteoporosis and is the type of bone most affected by medications used in the treatment of osteoporosis. A number of US FDA approved therapeutic agents are available to decrease bone resorption (anti bone resorbs). There are also a number of therapeutic modalities that increase bone formation (positive bone formers) (9).

Antiresorptive agents

Among the antiresorptive drugs, the predictive value of preclinical studies has been particularly well documented with the bisphosphonates.

Bisphosphonates

These are primary agents in the current pharmacological arsenal against osteoclast mediated bone loss due to osteoporosis, paget's disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy (23). Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate, a naturally occurring compound in which 2 phosphate groups are linked by esterification. It is the most commonly used treatment for established osteoporosis, inhibits osteoclast mediated bone resorption and reduces the risk of vertebral fracture. Maimoun et al cited that bisphosponates reduce bone loss in both the early and chronic phases of SCI, even though the demineralisation process cannot be stopped (24).

Oestrogen

Oestrogen is also approved by FDA for preventing osteoporotic fractures in post menoupausal women. The evidence suggests that oestrogen reduces the risk for vertebral and hip fracture; however, the effect of oestrogen on nonvertebral fracture risk is less clear.

Selective estrogen receptor modulators

Selective oestrogen receptor modulators have been developed to provide beneficial effects similar to those obtained with oestrogen, but without the adverse effects. The common SERM used are Tamoxifen, Raloxifen. Raloxifen has oestrogen agonist activity on the bones and lipids and an oestrogen antagonist effect on the breast and uterus.

Raloxifen is effective for reducing the incidence of vertebral fractures, but effectiveness at the hip has not been shown (25).

Salmon Calcitonin

Both intranasal and injectable forms of salmon calcitonin (Miacalcin) approved for the treatment of postmenopausal osteoporosis. Calcitonin inhibits bone resorption and is recommended for use in women with osteoporosis who are at least five years past menopause and cannot take other agents (20).

Adherence to osteoporosis treatment

The term ‘adherence’ comprises both compliance and persistence to treatment. ‘Compliance’ refers to how the medication is taken or quality of intake. ‘Persistence’ is defined as the time from initiation to discontinuation of treatment (26).

Anabolic agents (positive bone formers)

Parathyroid hormone

Parathyroid hormone, or fragments of the intact peptide molecule, may be of value in osteoporosis when administered parenterally. Such a usage is based on a presumed anabolic effect of parathyroid hormone when administered as a fragment, and it may be of value in established osteoporosis in terms of stimulating bone formation. The FDA approved the use of parathyroid hormone for the treatment of osteoporosis in 2002 (9).

Recombinant human parathyroid hormone (teriparatide)

Teriparatide (Foreto) is a recombinant human parathyroid hormone with potent bone anabolic activity (25).

It is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have a high risk of fractures and persons who have not improved on bisphosphonate therapy (9). In a dosage 20 mcg per day given subcutaneously for up to 2 years shows some benefits.

Fluoride

Fluoride as sodium salt has been introduced in the therapy of human osteoporosis without any well documented preclinical assessment of the relationship between bone mass and strength.

Experimental Therapies

Anabolic steroids

These currently experimental agents may actually have a beneficial effect on bone mass; their side effects include liver toxicity, masculinisation and an increased cholesterol level.

Testosterone

This may be of value in the treatment of osteoporosis in elderly men, particularly those with hypogonadism. Prostate and cholesterol status should always be checked when using testosterone (9).

Osteoporosis in spinal cord injury

Osteoporosis is a known consequence of SCI and occurs in almost every patient (27). The significance of osteoporosis after SCI is that it results in skeletal fragility and an increased risk of fractures. Complications from fractures lead to an increase not only in the associated morbidity and mortality, but also in the health care costs that they generate. These fractures predispose to exuberant callus that may cause pressure sores or may mimic infection or thrombosis.

Fractures are often complicated by profuse diaphoresis and an increase in spasticity (16). The porous nature of bones means that surgical fixation is often difficult; conservative treatment with plaster casts can result in pressure sores. Vestergaard et al found that low energy fractures were much more prominent in patients (19% of all fractures) than in controls (28). The fracture rate did not differ before the injury but increased after the injury to a constant level from the third year and forward. Fractures of the lower extremities were more prominent in patients than controls while fractures of the forearms and clavicles were absent among patients. Fractures were more frequent in female patients than in male patients with a family history of fracture.

The pattern of bone loss seen in SCI patients is different from that in osteoporosis, which occurs as a result of other aetiologies such as endocrine disease, nutritional disorders and drug-related factors (27).

Mechanism of bone loss in SCI

The effect of mechanical loading on bone tissue is an increase in bone formation on the periosteal bone surfaces, thus improving bone strength and reducing bone turnover and bone porosity (10). Consequently, mechanical loading can improve both bone size and shape and strengthen the bone tissue by improving tissue density.

Unloading

Kondo et al revealed that sympathetic nervous tone is mediating unloading induced bone loss via reduction in osteoblastic cell activity as well as enhancement in osteoclastic cell activity (29). SCI caused unloading and restricted movement of the lower limb joints for substantial periods of time and substantial muscle atrophy has been seen in SCI patients. Unloading may play an important role in the development of osteoporosis after SCI (30).

Neuronal changes- denervation

Innervation of bone is reported to have trophic effects on bone metabolism and a growing number of experimental and clinical studies indicate that innervations is important for bone remodelling (10). Similarly, SCI may lead to a significant decrease in innervation density and neuropeptides in the sublesional bones, thus distorting that balance of bone formation and resorption. In addition to the direct role of denervation on bone metabolism, denervation after SCI can cause disordered vasoregulation, thus affecting bone remodelling.

Hormonal changes

Although upper limbs are normally loaded and innervated, bone loss also occurs in the upper extremities in patients with paraplegia. Therefore, systemic hormones such as PTH, Vitamin D3, sex steroids, thyroid hormone and leptin may also be involved in bone loss following SCI (10).

Calcium balance

In general, SCI patients showed negative calcium balance with hypercalciuria after the injury (31). The increased osteoclastic bone resorption is mainly responsible for hypercalciuria following SCI. Exercises and ambulation significantly decreases the hypercalciuria and modifies the calcium balance in a positive direction, indicating that immobilisation may be an important factor resulting in this negative calcium balance (32).

PTH and Vitamin D

Secretion of PTH and increase in circulating 1,25 $(OH)_2$ vitamin D are subjected to control by negative feedback mechanisms related to serum calcium level (10). In addition, hypercalcemia after injury may lead to this PTH-vitaminD axis suppression in the acute phase of SCI.

PTH suppression in SCI patients is also associated with the degree of neurological impairment. In a cross sectional study, Machanick et al investigated serum PTH and 1,25 $(OH)_2$ vitamin D levels in SCI patients who were tested at a mean of 76.5 days post injury, and found that patients with complete SCI, when compared to those with incomplete injury, had a greater suppression of the PTH-Vitamin D axis (33). However, a reversal in parathyroid activity from 1 to 9 years after injury has been noted.

Effects on gonad function

Sex steroids play a pivotal role in regulating bone remodelling. Thus, a decrease in the circulating concentrations of these hormones increases osteoclast precursor formation in the bone marrow and thus increases the number of mature osteoclasts in cancellous bone (35). Maimoun et al reported recently that total testosterone and the free androgen index were significantly lower in SCI patients than in able bodied controls (36).

Management of osteoporosis in SCI

Morse et al cited that, although admission for osteoporotic fractures accounted for only 2.6% of the admissions, these hospitalisations resulted in longer lengths of stay than other admissions and individuals also required increased levels of assistance for transfers and self care during immobilisation of a fractured limb. Hence prevention of fractures would therefore decrease the health care costs and promote independence in this population (21).

Non Pharmacologic management

Prevention of falls

Morse et al also found that the most common cause of fracture in chronic SCI injury was falls, which may be difficult to prevent (21).

However, based on record review, 20% of fractures resulting in hospitalisation were due to transfer and wheel chair ambulation technique. It may be possible to reduce fracture risk by improving counselling and educating patients regarding limb protection during various self care activities and reinforce the importance of adequate doorway width for wheel chair clearance.

Standing-up and orthotic aided walking

The study by De Bruin et al indicates that early mobilisation led to no or insignificant loss of trabecular bone, where as the immobilised individuals showed a marked decrease when monitored for 25 weeks (37). In addition, the recent study by Alekna et al found that standing, particularly after 2 years, gave significantly higher BMD in legs, pelvis and the total body (38).

Physical exercise

The quality of evidence available for evaluation is poor (39). Miyahara et al found that the earlier the athlete started sports after injury, the higher the BMD of the legs, body, trunk and entire body (40). Further, a longer period of athletic career after restarting was significantly related to higher leg BMD.

Functional electrical stimulation

Functional electric stimulation is a method of exercise that has been employed in the SCI population that has demonstrated some success in improving muscle, with less conclusive evidence that it has a positive effect on bone (17). Be dell et al demonstrated that there was no significant increase in bone density in the hip parameters of chronic SCI patients after functional electrical stimulation induced lower extremity cycling, though a positive trend was observed in the lumbar spine (41).

Gianggregario et al demonstrated that 9 months of thrice weekly FES cycle ergometry failed to increase BMD at the femoral neck, distal femur and proximal tibia in individuals with complete SCI (17).

Low intensity pulsed ultrasound

Naruse et al demonstrated that low intensity, pulsed ultra sound, which has been clinically used to accelerate the healing process of fractured bone, induces a direct anabolic reaction of osteogenic cells, leading to bone matrix formation (42). Warden et al applied specific ultra sound at the calcaneum for 6 weeks in young subjects with 1-6 month histories of complete SCI (43). The results showed that low intensity pulsed US were unable to protect against SCI induced calcaneal bone demineralisation. Further investigations are needed.

Pharmacological Management

The physiopathological data have shown that bone demineralisation in patients with SCI can be principally attributed to an alteration of the bone remodelling process that dramatically favours an increase in bone resorption. Drug treatment thus mostly consists of substances that inhibit osteoclast cell activity (24).

AIMS AND OBJECTIVES

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Determine incidence of vertebral osteoporosis following acute spinal cord injury.

MATERIALS AND METHODS

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Study design: Descriptive study

Patients with tetraplegia or paraplegia getting admitted under the department of Physical medicine and Rehabilitation, Christian Medical College Hospital, Vellore for rehabilitation within 2 weeks following acute spinal cord injury were included in this trial.

20 patients aged between 20 to 40 years including both male and female admitted within 2 weeks following traumatic acute spinal cord injury with paraplegia or tetraplegia were included in this study and observed over a period of 20 weeks.

The study in detail was presented to the ethical review committee of the CMC Hospital and permission was obtained. Before recruiting the patients for this study, they were explained about the nature of the injury, nature of the study and details of the study plan. An informed consent to participation was obtained from all patients in accordance with Helsinki ll Declaration.

Inclusion and Exclusion criteria

1. Inclusion Criteria:

i. Any patient with acute traumatic SCI (paraplegic or tetraplegic) who is admitted within 2 weeks of traumatic spinal cord injury.

ii. Age group of 20-40 years.

2. Exclusion Criteria:

a. Patients with internal fixation for the vertebral fractures.

b. Patients with any chronic illness like Chronic Renal Failure (Contracted kidneys in the ultrasound and serum creatinine >1.5 mg%), history of malabsorption etc.

c. Patients taking drugs regularly for other diseases, which are likely to develop osteoporosis (e.g. steroids, anti-inflammatory agents etc.)

d. Patient who is not able to give informed consent.

Immediately after the admission a detailed history and clinical evaluations were done. A baseline bone mineral density was done at the time of admission. In addition to the routine investigations the following investigations were done to rule out other possible causes of secondary osteoporosis.

1. Serum calcium & serum phosphorus
2. 24- hour urinary calcium
3. Serum creatinine
4. Serum total protein and albumin
5. Serum alkaline phosphatase
6. PCV
7. Serum sodium, potassium, and bicarbonate

8. Ultrasound abdomen

9. X-ray thoraco lumbar spine

Sample size

Power calculation shows, if we study 20 patients, we have 80% power to detect 30 mg/cc change in BMD from normal and >90% power to detect >50 mg/cc change in BMD. Normal BMD values and standard deviation of this value was obtained from QCT data.

Measurements:

Spinal bone mineral density was obtained on all patients within 2nd week following acute spinal cord injury. At the end of 20 weeks the scan was repeated to determine the change in bone mineral density. A second-generation single energy Wipro CT Sytec-4000 machine used for measurement of Quantitative computerized tomogram (QCT) Phantom values throughout the study period. Same Radiologist was authorized for the procedures throughout the study period. The Radiologist was blinded from knowing whether it was first or second QCT scan to prevent bias. The phantom values were converted into bone mineral density values for age and sex matched using QCT WIN software and print out was obtained.

QCT measurement procedures

Patients with Spinal Cord Injury (Within 2 weeks following injury) were admitted following fulfilment of inclusion /exclusion criteria were subjected for first QCT analysis of spinal bone mineral density (QCT 1). All technical parameters were followed according to CT scanning instructions from user's guide. Solid cylindrical calibration phantom using reference samples (0, 50,100,200 mg/cc) used for collecting phantom values.

Patient positioning procedures

The patient set -up procedure was similar to a lumbar spine series except that the patient was positioned on the QCT calibration phantom during the scans. The procedure was begun by placing the calibration phantom on the scanner cradle near the center of the scan range.

The phantom placed within the cushion cutout with correct side up. Placed the bolus bag lengthwise on the phantom with the white insulated side up (this provides thermal insulation for patent comfort).

Figure 2: QCT equipment

Figure 3: QCT table and calibrated Phantom

The patient was positioned on the phantom, bolus bag, and cushion with the end of phantom approximately at L5/S1, so L4 through T10 would be over the phantom. Thick clothing was removed and elevating the knees helped to flatten the back and achieve close contact with the phantom. A bolus bag (jell pack) was placed between the patient and the calibration phantom. It was used to remove air gaps that produce streaks, scatter and edge effects, which degrade the quantitative results. After fulfilling the various parameters according to user's guide a scout film was taken and identified the vertebrae to be scanned. . A 10 mm thick slice cut through the exact center of the vertebrae at an angle parallel to the endplates. Bone densities for 6 vertebral bodies (from T11 to L4) and phantom values and averaged to obtain a single result for the patient

Vertebral ROI placement:

The vertebral ROI optimized to obtain the maximum (ideally 3-4 cm^2) sample of trabecular bone and 2 pixels away from the cortical rim. The calibration phantom contains four samples of materials, which will appear on the CT image with 3 visibly different densities and an apparent blank space at the water (0 mg/cc) position. The known concentrations of calcium hydroxyapatite in the rods are (beginning with the densest [white] cylinder on the CT viewing monitor): 200 mg /cc, 100 mg/cc, 50 mg/cc, and 0 mg/cc.

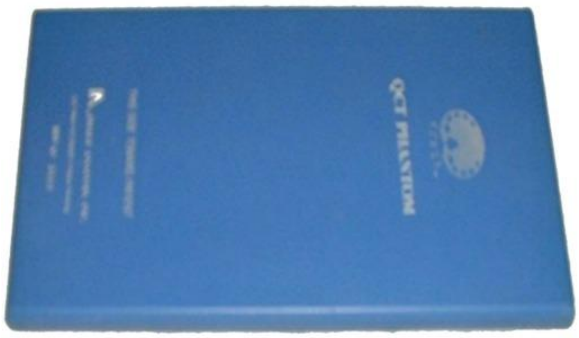

Figure 4: Calibrated Phantom

All data are entered in QCT win software and displayed on the screen to plot the individual BMD readings of each vertebra compared to the reference curve by age .The mean reference values, as a function of age, display as the central curve.

The two additional outer curves represent +/- 1 standard deviation. Fracture prevalence is also shown by the colored regions where red is high, yellow is moderate, and green is low risk for fracture. The comparison of serial exams shows a graph of BMD results for the patient on repeated exams. The table lists each exam date, the mean BMD for each exam, the BMD change in mg/cc from the last exam.

Data Collection:

BMD values were obtained at the 2^{nd} week and 20^{th} weeks following spinal cord injury using QCT Scan. A standardized pro-forma was used to enter patient information. This was entered in a computerized database.

Data Analysis:

The **primary outcome** was the change in the bone mineral density. The differences between the first and second QCT was ascertained. The differences were compared for means of two independent samples, first and second QCT was compared for means of two correlated samples (paired t test). The results were analyzed using SPSS PC^{+} for windows with the help of a qualified Clinical epidemiologist.

RESULTS

RESULTS

DEMOGRAPHY

Twenty acute spinal injured patients who fulfilled the selection criteria were recruited into the study.

Table 1: Demography

Demography				
Age	Mean	31.5 years	Range	21 to 40
Gender	Male	18	Female	2
Type of trauma	Fall	14	Motor vehicle accident Industrial accident	4 2
Neurological level	Tetraplegia	10	Paraplegia	10
ASIA score	Complete	10	Incomplete	10
Tone	Spastic	14	Flaccid	6

Age distribution

The mean age of patients recruited was 31.5 years, ranged between 21 to 40 years.

Gender distribution

There were eighteen males and two female patients participated in the study.

Causes of spinal cord injury

Among 20 patients recruited in the study fourteen patients sustained injury due to fall, four from motor vehicle accident and another two by industrial accident.

Neurological level

There were ten patients each, grouped as tertaplegic and paraplegic respectively among the total twenty patients who were consented for the study.

Completeness of spinal cord injury according to ASIA score

There were ten complete and equal amount of incomplete patients were participated in the study.

Tone

Among twenty patients participated in the study, fourteen developed spasticity and remaining six were continue to flaccid.

Associated injuries and other morbidities

One patient developed haemothorax which was managed by chest drain. Three patients developed doppler ultra sound confirmed deep vein thrombosis and managed by oral anticoagulants. Two patients sustained long bone fractures of lower limbs simultaneously and managed conservatively. One patient sustained de-glove injury of lower limb and scrotum which was also managed conservatively. One patient diagnosed to have bipolar affective disorder after inclusion and another patient developed tonic-clonic seizures. These patients were managed with oral medications. One patient incidentally found to have vertebral hemangioma extending from T11 to L4. All the patients continued to participate in the study till 20 weeks.

Mobility at twenty weeks

After completing 3 months immobilisation of spine, encouraged the patients for active mobilisation. At twenty weeks, among twenty patients three patients walked without any aid or appliances, eight walked with help of orthoses, three were ambulant using wheel chair and six patients were continued to be on bed rest.

CHANGE IN BONE MINERAL DENSITY

Variation between first and second BMD from the standard age and sex matched normal BMD values

First BMD value in eighteen patients among twenty was at or above the standard age and sex matched normal. Two patients at first QCT itself was more than 1 standard deviation (SD) but less than 2 SD below age and sex matched normal (osteopenic range). These two patients at the end of 20 weeks fall 5 and 14 mg/cc respectively. Among those 18 patients, twelve were maintained the BMD value above normal at the end of 20 weeks. Six patients among above 18 patients showed significant fall in BMD from age and sex matched normal at the end of 20 weeks. Five patients among this 6 had a fall more than or equal to 1 SD (1 SD=27 mg/cc) below age and sex matched normal (osteopenic range) and one had a fall less than 1 SD. Among 20 patients in the study two patient's first BMD value was very much below normal and continued to fall at the end of 20 weeks.

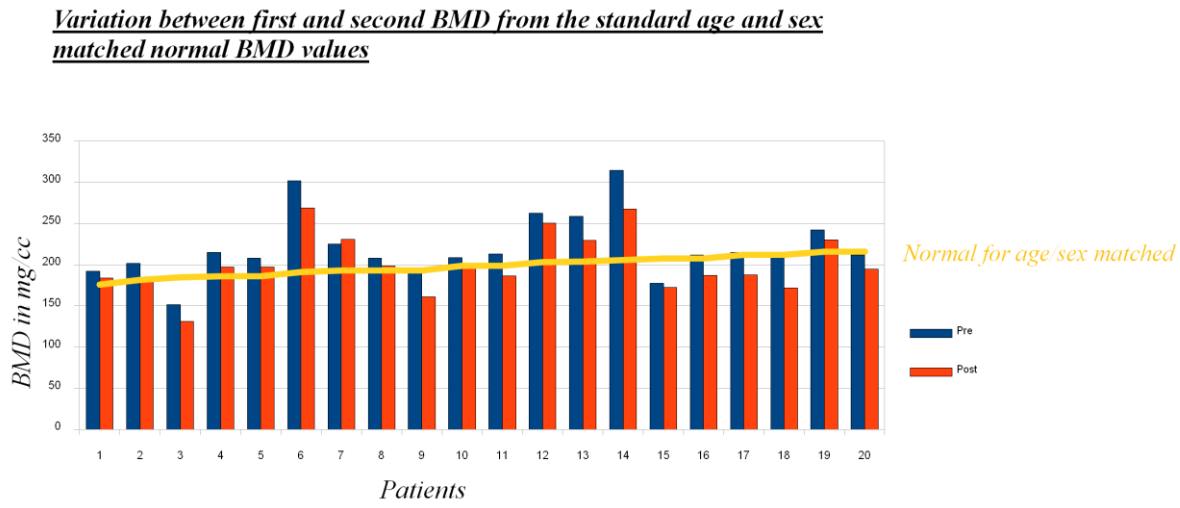

Figure 5: Change in BMD from age & sex matched normal

Change in BMD over 20 weeks

On evaluating for fall in BMD from the first QCT to second without comparing to age and sex matched BMD, following observation was made.

The mean difference of BMD change (fall in BMD) among 19 patients was 19.76 mg/cc (ranges 5 to 47 mg/cc). One patient showed rise in BMD from first QCT (5.8 mg/cc).

Statistics

Comparison of means of two correlated samples (first and second BMD) –

The paired t-test

The critical ratio t follows a t-distribution with 19 degrees of freedom. The t- distribution for 19 degrees of freedom gives the 5% level as 2.093 and 1% level as 2.861. The observed critical ratio value 6.8 is more than 1% level. The test provides evidence to say that there is significant difference between first and second QCT value for change in BMD **(P- value is more than 0.001)**.

Comparison of means of two independent samples – Tetraplegic and Paraplegic BMD

The critical ratio t follows a t-distribution with 18 degrees of freedom. The t- distribution for 18 degrees of freedom gives the 5% level as 2.101and 1% level as 2.878. The observed critical ratio value 0.2509 is less than 5% level. The test provides evidence to say that there is no significant difference in BMD value of first and second QCT among tetraplegic and paraplegic **(p-value less than 0.05)**.

DISCUSSION

DISCUSSION

Bone is constantly remodelling, with an increase in bone resorption, typically followed within 30 to 40 days by the process of bone formation. With normal bone remodelling, there is no net change in the amount of bone mass present in young adults (9). In most forms of osteoporosis a disruption of bone remodelling occurs. The measurement of bone mineral content or density forms the basis for an operational definition of osteoporosis. The operational definition of osteoporosis is based on the distribution of skeletal mass in young healthy individuals by WHO (14). The relationship between bone mineral density and fracture risk is continuous, and an estimate of bone mineral density therefore provides an effective assessment of fracture risk (11).In any condition that causes immobilisation, loss of bone occurs and is correlated to the severity of unloading. The incidence of lower extremity fractures in SCI patients was found to be ranging from 1 to 34% (28, 44).

In view of the importance of trying to prevent osteoporosis, a common complication in the SCI population (16), it was decided to quantify the incidence of vertebral osteoporosis in this study population.

QCT allows for a three-dimensional true density measurement of bone without superimposition of other tissues and therefore provides exact three-dimensional anatomic localisation of the measured tissue (18). Bone density can be calculated separately in trabecular and cortical bone compartments. Selective measurement of high turnover trabecular bone, such as the central portion of the vertebral body, is of some advantage because it excludes cortical bone and extra osseous calcification. QCT results are expressed as mgm of K_2HPO (dipotassium hydrogen orthophosphate) per cubic cm of bone volume, reflecting a true three dimensional density rather than the two dimensional area of DXA.

In this study, 20 acute spinal cord injured (SCI) patients, who fulfilled the inclusion criteria, were recruited. They were observed for 20 weeks to determine the incidence of occurrence of vertebral osteoporosis.

There are several risk factors for secondary osteoporosis that could have affected the outcome of this study. The relevant risk factors include age, gender, neurological lesion and immobility and these are explored further below.

Age

SCI in Western populations occurs primarily in young adults, with more than half occurring in persons 16 to 30 years of age, and males account for about 80% of cases (45). The incidence and prevalence of osteoporosis consistently increases with age. During growth the trabecular bone of the skeleton matures to its peak density at around 16 to 20 years of age and then begins to decline gradually (47). After a plateau in BMD around ages 30 to 45 years, a rapid decline in BMD occurs soon after menopause in women, followed by a gradual decline with age in both sexes (46). In this study the mean age of all the patients was 31.5 years (range 21 to 40) and therefore all the patients could be considered to be within this plateau period. Ross PD (46) in his review stated that, by definition, approximately 15% of young adults in the USA have osteopenia and only about 0.6% has osteoporosis. In this study, based on an Indian population, 2 (10%) of the patients at the start of the study, and 5 (25%) of the patients at the end had osteopenia; none of the patients had developed osteoporosis.

Roberts et al (16) followed up 30 acute SCI patients, average age 28.6 years (range from 13.8 to 66.3 years), and they observed that the markers of bone resorption showed significant increase six months following injury, but markers of bone formation showed only a minor rise.

Garland DE et al (12) observed in his radiological studies, among SCI, that approximately one third of bone mineral is lost within 3 – 4 months of SCI, after which time the loss slows. Naftchi et al (48) studied twenty acute SCI patients with a mean age of 25 years (range from 19 to 40 years) and they also observed an increase in bone resorption markers in all patients.

Szollar et al (49, 50) in two studies compared 263 and 240 chronic SCI patients respectively with 92 and 80 able bodied individuals. The spinal cord injured patients were at various times post injury (1 to 59 years), their mean age was 48.8 years (range from 20 to 78 years) and the able bodied individuals had a mean age of 51.1 years (range from 24 to 76 years). Kannisto et al (47) studied thirty five adults who had sustained their injury in childhood, the median age at the time of injury was 12.9 years (range from birth to 17.1 years), the median age at the time of study was 31 years (range from 18 to 63 years) and the median time period from the injury was 19 years (range from 1.5 to 57 years). They observed a reduction in bone mineral density in the femoral region. Biering-Sorenson et al (51) studied twenty six patients (age range from 20 to 65 years) who had sustained their injury 2 to 25 years ago and observed a greater bone mineral content (BMC) reduction in the femur and tibia rather than the lumbar region. Leslie et al (52) looked at fourteen SCI patients, whose average age was 32.4 years, and the lumbar bone mineral density was found to be well preserved. Needham-Shropshire et al (53) studied sixteen SCI patients whose average age was 28.8 years and mean duration post injury was 3.8 years. Demirel et al (3) studied forty one SCI patients and their mean age was 35.8 years (range from 19 to 49 years).

Gender

There were 18 males and 2 females included in the study. This male: female ratio suggests that males are affected more commonly than females in traumatic SCI in India, however, since this is a hospital based study rather than a community based one, one cannot be categorical about the gender ratio.

Similar gender differences were observed in other studies (3, 16, 45, 47, 48, 50, 51, 52, 53). In the general population bone loss begins earlier and proceeds more rapidly in females than males, with an accelerated phase in postmenopausal years (54). As the numbers of females in this study population is very small, it is not possible to evaluate the difference in osteoporosis with regard to gender in the spinal cord injured population.

Causes of spinal cord injury

In this study the commonest cause of SCI was due to fall (n=14, 70%) from a height, where as in Western populations the majority of the SCI was due to motor vehicle accidents (45). Motor vehicle accidents are becoming more common in our country as well; despite this it is interesting that only 4 of the patients (20%) in this study had injuries secondary to motor vehicle accidents.

Neurological Lesion

There were 10 tetraplegic and 10 paraplegic patients and equal numbers of incomplete and complete SCI patients in this study group. There were 14 spastic patients and 6 flaccid patients. There was significant improvement (at least 1 neurological segment) in neurological status in all patients.

Associated injuries and other morbidities

There were a few patients with associated illnesses and injuries in this group that could have affected their bone mineral density. Some injuries prolonged the period of immobilisation, and some illnesses required drugs, which could have affected the BMD. One patient had a haemothorax that did not interfere with his mobilisation. Another patient had a de-glove injury of left lower limb, this delayed his mobilisation but he did not drop his BMD value into the osteoporotic range.

Three patients developed deep vein thromboses confirmed by Colour Doppler Ultrasound examination. All of them were put on intravenous heparin for 24 hours and then started on oral Nicoumalone, (Sintrom) a coumarin derivative. 15000 units heparin for a period of 6 months or more has been reported to cause osteoporosis (55) but there are no reports that Sintrom causes osteoporosis.

One patient was diagnosed as having a bipolar affective disorder and was treated with oral Risperidone, an anti psychotic drug, a benzisoxazole derivative. Continuous use of this has not been reported to produce osteoporosis (56). Another patient was diagnosed to have generalised tonic clonic seizures and was managed by oral carbamazapine. Phenytoin sodium is reported to produce osteoporosis, but carbamazapine is not (56). One female tetraplegic was found to have a haemangioma in the vertebral body extending from thoracic 11 to lumbar 4 on her spine QCT scout film. This could be the reason for her initial very low BMD value (osteopenic range) but her drop from the first to the second QCT, BMD (20.5 mg/cc) was close to the average drop (19.76mg/cc).

Metabolic responses to SCI

After an acute SCI, a patient's early metabolic response is presumably influenced by the hyper metabolism related to the injury and includes a negative nitrogen balance (57). Several speculations have been made concerning the aetiology of this negative nitrogen balance. For example immobility can cause wasting and break down of muscle protein (57), which is detected by increased urinary nitrogen output, and leads to organ failure and death. It was demonstrated that obligatory nitrogen losses after SCI persists for approximately 7 weeks post injury. Conversely the negative nitrogen balance found post injury may cause a loss of lean muscle mass (57) and so an excess production of metabolic acids. Denervation atrophy has also been hypothesised as being responsible for this phenomenon (57).

Acute SCI is often associated with injuries to other organ systems and is compounded by complications such as respiratory insufficiency and infection. These and the nutritional status will affect the catabolic status of the patient.

A delayed chronic phase of metabolic response that is characterised by an obligatory loss of lean body mass, a marked reduction in substrate use, and decreased metabolic activity has been observed and extensively studied in SCI (57, 58). In spinally injured patients, the nitrogen balance remains negative for a longer time frame; presumably partly due to the denervation of the lean muscle mass. Other factors may contribute to this including the reduced level of mobility found in SCI patients. Rodriguez et al (57) concluded that acute immobilisation could, in part, be a cause of acute post-injury increase in nitrogen which observed in paralysed patients and SCI patients generally remain less mobile than the general population.

In this study, the mean difference of BMD change (fall in BMD) was 19.76 mg/cc (ranges 5 to 47 mg/cc). The average drop in BMD 19.76 mg/cc from first to second QCT for all the patients was statistically significant ($p > 0.001$), consistent with Roberts et al findings (16). None of the patients BMD's dropped to the osteoporotic range. When one considers fracture threshold at an equivalent mineral density of about 110mg/cc (59), the incidence of osteoporosis in this study population of acute spinal cord injured patients is zero. However 2 of the patients (10%) in the beginning of the study and 5 of the patients (25%) at the end had osteopenia but no patient in this group dropped their BMD to an osteoporotic level at the end of 5 months. This may be because it is too early to detect osteoporosis, but at a later stage it may be that the BMD continues to drop and will eventually reach the osteoporotic range.

Tetraplegia, paraplegia and bone turnover

The literature relating to potential differences in bone turnover between tetraplegics and paraplegics is conflicting (3, 16, 52). The failure to clearly demonstrate differences between tetraplegics and paraplegics may reflect heterogenecity of these populations; patients with low tetraplegia can have sufficient use of their arms to propel themselves in a wheel chair, as do paraplegics. Thus functionally, some paraplegics and tetraplegics may not be very different, and their bone turnover would not be expected to be dissimilar.

There was no difference in the first and second QCT (BMD) in paraplegics and tetraplegics in this study. There was no significant difference in BMD value of first and second QCT among tetraplegic and paraplegic ($p < 0.05$). Roberts et al (16) found no significant difference in absolute values of bone turnover markers between paraplegic and tetraplegics. They found one of the bone turnover markers, pyridinoline, was greater in tetraplegics but other markers did not show any increase. Pyridinoline is a non-specific marker as it is also found in other connective tissue. As tetraplegics have more soft tissue turnover when compare to paraplegics, the pyridinoline level was naturally higher in tetraplegics. In contrast, deoxypyridinoline and N-telopeptide are more bone specific. Roberts et al concluded that there was a suggestion and not conclusive proof that quadriplegics may have a greater bone turnover than paraplegics.

Spasticity and BMD

Among twenty patients participated in the study, fourteen developed spasticity and remaining six were continue to be flaccid. There was no difference in the BMD with respect to tone. Comarr et al observed that lower motor neuron lesions were associated with a higher fracture risk than upper motor neuron lesions (60). Biering-Sorensen et al found that spasticity had no significant influence on the bone mineral content (51).

Leslie et al observed a weak positive association between femoral neck BMD and the Ashworth spasticity score but this was not statistically significant (52).

Mobility and BMD

There is evidence that the loss of gravitational loading plays a significant role as a stimulus in initiating the early resorptive state (52). Muscular loading of the bones has also been thought to play a role in the maintenance of bone density. In this study there was no difference in the fall in BMD between those who were walkers, those who were wheelchair users and those who were bed bound. Biering- Sorensen et al observed that the average bone mineral content of the lumbar spine in spinal cord injured was a little higher than that of normal and concluded that the lumbar spine continues to be loaded while sitting on a wheel chair (51). This increase in lumbar spine BMD compared to the normal age sex matched BMD was not found in this study. They also did not find any significant difference in the BMD of the long bones or the vertebral bones in those using long leg braces every day. They concluded that the reason for not observing any difference in BMD between users and non-users of long leg braces is that long leg braces do not give rise to very much weight bearing on the long bones and the weight, to a great extent, is transmitted through the braces.

LIMITATIONS OF THE STUDY

LIMITATIONS OF THE STUDY

- This study was designed to evaluate the vertebral osteoporosis in persons with acute spinal cord injury at the end of 20 weeks. Since spinal cord injury is a chronic disabling condition, continuing measurements at 1 year and beyond may give us a true picture of the extent of the ongoing vertebral osteoporosis.
- Nearly all patients demonstrated a drop in bone mineral density, none of them dropped into osteoporotic range when measured by single energy quantitative computerised tomography (SEQCT). It is believed that dual energy quantitative computerised tomography (DEQCT) is more accurate; therefore using a more sensitive and accurate method like DEQCT may give us different results. However DEQCT exposes the person to a higher dose of radiation, which is a drawback.
- A greater number of patients would have increased the reliability of the conclusions and the conclusions drawn from the subgroups like gender, level of lesions etcetera.

CONCLUSION

CONCLUSION

- In the 20 patients with acute spinal cord injury studied, at 20 weeks after injury 95% showed decrease in their bone mineral density, 25% were osteopenic and none were osteoporotic. The incidence of vertebral osteoporosis in persons with acute spinal cord injury in this study is zero.
- At 20 weeks the bone mineral density in persons with acute spinal cord injury was not affected by neurological status, mobility status or muscle tone.

BIBLIOGRAPHY

Bibliography

1. Garland DE, Stewart CA, Adkins RH, et al. Osteoporosis after spinal cord injury. *J Orthop Res.* 1992; 10:371–378.
2. Biering-Sorensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. *Eur J Clin Invest.* 1990; 20:330–335.
3. Demirel G, Yilmaz H, Paker N, Onel S. Osteoporosis after spinal cord injury. *Spinal Cord.* 1998; 36: 822–825.
4. Frey-Rindova P, de Bruin ED, Stussi E, Dambacher MA, Dietz V. Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. *Spinal Cord.* 2000; 38:26–32.
5. De Bruin ED, Dietz V, Dambacher MA, Stussi E. Longitudinal changes in bone in men with spinal cord injury. *Clin Rehabil.* 2000; 14:145–152.
6. Eser P, Frotzler A, Zehnder Y, Schiessl H, Denoth J. Assessment of anthropometric, systemic, and lifestyle factors influencing bone status in the legs of spinal cord injured individuals. *Osteoporos Int.* 2005; 16:26–34.
7. Bonjour JP, Ammann P, Rizzoli R. Importance of peripheral studies in the development of drugs for treatment of osteoporosis: a review related to the 1998 WHO guidelines. Osteoporos Int. 1999; 9(5): 379-393.
8. Grampp S, Jergas M, Gluer C C et al: Radiologic Diagonosis of osteoporosis. Radiologic Clin of N AM.1993; 31 (5): 1133 – 1145.
9. De Lisa JA, Gans BM,Walsh NE. Physical Medicine and Rehabilitation: Principles and Practice, 4th Edition, 2005. P. 699-717.

10. Jiang SD, Jiang LS, Dai LY. Mechanism of osteoporosis in spinal cord injury. Clin Endocrinol (Oxf). 2006 Nov; 65 (5): 555-565
11. WHO. World Health Organisation guidelines for preclinical evaluation and clinical trials in osteoporosis Geneva 1998.
12. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ et al. Osteoporosis after spinal cord injury. J Orthop Res. 1992 May 10 (3): 371-378.
13. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser 2003; 921:1-164, back cover.
14. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Technical Report Series, No.843 study group. World Health Organization, Geneva, WHO, 1994.
15. Malhotra N, Mithal A. Osteoporosis in Indians. Indian J Med Res. 2008 Mar; 127 (3): 263-268
16. Roberts D, Lee W, Cuneo RC, Wittmann J, Ward G, Flatman R et al. Longitudinal study of bone turnover after acute spinal cord injury. J Clin Endocrinol Metab. 1998 Feb; 83 (2): 415-422
17. Gianggregorio L, McCartney N. Bpne loss and muscle atrophy in spinal cord injury: epidemiology, fracture prediction and rehabilitation strategies. J Spinal Cord Med. 2006; 29 (5): 489-500.
18. Grampp S, Jergas M, Gluer C C et al: Radiologic Diagonosis of osteoporosis. Radiologic Clin of N AM.1993; 31 (5): 1133 – 1145.
19. Marshall D, Johnell O, Wedel H. Meta analysis of how well measures of bone mineral density predict occurrence of osteoporosis fractures. BMJ 1996 May 18; 312 (7041): 1254-1259.

20. Zizic TM. Pharmacologic prevention of osteoporotic fractures. Am Fam Physician. 2004Oct 1; 70(7): 1293-300.
21. Morse LR, Battaglino RA, Stolzmann KL, Hallet LD, Waddimba A, Gagnon D et al. Osteoporotic fractures and hospitalisation risk in chronic spinal cord injury. Osteoporos Int. 2009 mar; 20(3): 385-392.
22. Tinetti ME. Clinical practice: Preventing falls in elderly persons. N Eng J Med. 2003 Jan 2 ; 348(1): 42-49.
23. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008Sep; 83(9): 1032-045.
24. Maimoun L, Fattal c, Micallef JP, Peruchon E, Rabischong P. Bone loss in spinal cord injured patients: from pathophysiology to therapy. Spinal Cord. 2006 Apr; 44(4):203-210.
25. Sweet MG, Sweet JM, Jeremiah MP, Galazka SS. Diagnosis and treatment of osteoporosis. Am Fam Physician. 2009 Feb 1; 79(3):193-200
26. Rossini m, Bianchi G, Di Munno O, Giannini S, Minisola S, SinigagliaL et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int. 2006;17(6): 914-921.
27. Jiang SD, Dai LY, Jiang LS. Osteoporosis after spinal cord injury. Osteoporos Int. 2006 Feb; 17(2): 180-192.
28. VestergaardP, Krogh K, Rejnmark L, Mosekilde L. Fracture rate and risk factors for fractures in patients with spinal cord injury. Spinal cord. 1998 Nov; 36(11): 790-796.
29. Kondo H, Nifuji A, Takeda s, Ezura Y, Rittling SR, Denhardt DT et al. Unloading induces osteoblastic cell suppression and osteoclastic cell activation to lead to bone loss via sympathetic nervous system. J boil Chem. 2005 Aug 26; 280(34): 147-156.
30. Takata S, Yasui N. Disuse osteoporosis. J Med Invest. 2001 Aug; 48(3-4): 147-156.

31. Maynard FM, Imai K. Immobilisation hypercalcemia in spinal cord injury. Arch Phys Med Rehabil. 1977 Jan; 58(1): 16-24.
32. Kaplan PE, Gandhavadi B, Richards L, Goldschmidt J. Calcium balance in paraplegic patients: influence of injury duration and ambulation. Arch Phys Med Rehabil. 1978 Oct; 59(10): 447-450.
33. Mechanick JI, Pomerantz F, Flanagan S, Stein A, Gordon WA, Ragnarsson KT. Parathyroid hormone suppression in spinal cord injury patients is associated with the degree of neurologic impairment and not the level of injury. Arch Phys Med Rehabil. 1997 Jul; 78(7): 692-696.
34. Bauman WA, Zhong YG, Schwartz E. Vitamin D deficiency in veterans with chronic spinal cord injury. Metabolism. 1995 Dec; 44(12): 1612-1616.
35. Jilka RL, Hangoc G, Girasole G, Passeri G, Williams DC, Abrams JS et al. Increased osteoclast development after estrogen loss: mediation by interleukin 6. Science. 1992 Jul3; 257(5066): 88-91
36. Maimoun L, Lumbroso S, Paris F, Couret I, Peruchon E, Rouays-Mabit E et al. The role of androgens or growth factors in the bone resorption process in recent spinal cord injured patients: a cross sectional study. Spinal Cord. 2006 Dec; 44(12): 791-797.
37. De Bruin ED, Frey-Rindova P, Herzog RE, Dietz V, Dambacher MA, Stussi E. Changes of tibia bone properties after spinal cord injury: effects of early intervention. Arch Phys Med Rehabil. 1999Feb; 80(2): 214-220.
38. Alekna V, Tamulaitiene M, Sinevicious T, Juocevicius A. Effect of weight bearing activities on bone mineral density in spinal cord injured patients during the period of the first 2 years. Spinal Cord. 2008 Nov; 46(11): 727-732.

39. Biering-sorenson F, Hansen B, Lee BS. Non pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. Spinal Cord. 2009 Jul; 47(7): 508-518
40. Miyahara k, Wang DH, Mori k, Takahashi K, Miyatake n, Wang BL et al. Effects of sports activity on bone mineral density in wheel chair athletes. J Bone Miner metab. 2008; 26(1): 101-106
41. Be Dell KK, Scremin AM, Perell KL, Kunkel CF. Effects of functional electric stimulation induced lower extremity cycling on bone density of spinal cord injured patients. Am J Phys Med Rehabil. 1996 Jan-Feb; 75(1): 29-34.
42. Naruse K, Mikuni-Takagaki Y, Azuma Y, Ito m, Oota T, Kameyama K et al. Anabolic response of mouse bone marroe derived stromal cell clone ST2 cells to low intensity pulsed ultrasound. Biochem Biophys Res Commun. 2000 Feb 5; 268(1): 216-220.
43. Warden SJ, Bennell KL, Matthews B, Brown DJ, McMeeken JM, Wark JD. Efficacy of low intensity pulsed ultra sound in the prevention of osteoporosis following spinal cord injury. Bone. 2001 Nov; 29(5): 431-436.
44. Frisbie JH. Fractures after myelopathy: the risk quantified. J Spinal Cord Med. 1997Jan; 20(1): 66-69.
45. Staas WE Jr, Formal CS, Freedman MK et al: Spinal cord injury and spinal cord injury medicine. In Delisa JA,ed. Rehabilitation Medicine principles and practice ,Third Edition, Lippincot-Raven publishers,1998: 1261 - 1262.
46. Ross P D: Osteoporosis - Frequency, consequence and risk factors. Arch Intern Med. 1996; 156: 1399 - 1411.
47. Kannisto M, Alaranta H, Merikanto J et al: Bone mineral status after pediatric spinal cord injury. Spinal cord. 1998; 36: 641 - 646.

48. Naftchi N E, Viau A T, Sell G H, et al: Mineral metabolism in spinal cord injury. Arch Physical Medicine and Rehabilitation. 1980; Vol 61: 139 – 142
49. Szollar SM, Martin E M E, Parthemore J G et al: Demineralization in tetraplegic and paraplegic man over time. Spinal cord.1997; 35: 223 - 228.
50. Szollar SM, Martin EME, Parthemore JG et al: Densitometric patterns of spinal cord injury associated bone loss. Spinal cord 1997; 35: 374 - 382.
51. Biering-sorenson F, Bohr H, Schaadt O: Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesion. Paraplegia.1988; 26: 293 - 301.
52. Leslie W D, Nance P W: Dissociated hip and spine demineralisation: A specific finding in spinal cord injury. Arch Phys Med Rehabil. 1993; 74: 960 - 964.
53. Needham -Shropshire B M, Broton J G, Klose J et al: Evaluation of a training program for persons with SCI paraplegia using the Parastep^{R} 1 ambulation system: Part 3. Lack of effect on bone mineral density. Arch Phys Med Rehabil. 1997; 78: 799 - 803.
54. Matkovic V, Colachis III SC, Ilich JZ: Osteoporosis: its prevention and treatment. In Braddom RL, Ed. Physical medicine and rehabilitation, First Edition, WB Saunders company, 1996: 851 - 875.
55. Satoskar RS, Bhandarkar SD, Ainapure SS: Drugs acting on blood and blood forming organs.Pharmacology and pharmacotherapeutics, Fourteenth edition, Popular Prakasshan publishers, 1995: 415.
56. British national formulary: Drugs used in psychoses and related disorders. Number 32, September 1996; 4.2: 165, 205, 208.
57. Rodriguez DJ, Benzel E C, Clevenger F W: The metabolic response to spinal cord injury. Spinal Cord. 1997; 35: 599 - 604.

58. Uebelhart D, Domenech B D, Roth M, et al: Bone metabolism in spinal cord injured individuals and in others who have prolonged immoblisation. A review. Paraplegia 1995; 33: 669 - 673.
59. Hayes W C, Piazza S J, Zysset P K: Biomechanics of fracture risk prediction of the hip and spine by quantitative computed tomography. Rad Clin N Am. 1991; 29 (1): 1 - 18.
60. Comarr AE, HutchinsonRH, Bors E: Extremity fractures of patients with spinal cord injuries. Am J Surg. 1962; 103: 732 – 739.

DATA SHEET

Sr No	Hosp No	Age	Gender	Neurological level & ASIA Score	Age/sex matched normal BMD	First BMD	Second BMD	Change in BMD at end of 20 weeks
1	464161B	35	M	C6 **B**	193.3	194.9	161.1	-33.8
2	464395B	25	M	C5A	211.9	215.1	187.5	-27.6
3	472464B	27	M	L2B	208.2	177.6	172.6	-5
4	523046B	35	M	T11B	193.3	302.2	268.6	-33.6
5	496033B	30	M	T7A	202.6	262.7	250.3	-12.4
6	539254B	40	F	T11B	178.6	192.1	183.8	-8.3
7	543206B	31	M	T11A	200.8	213.3	186.7	-26.6
8	539851B	38	M	C5B	187.8	208.0	197.3	-10.7
9	546711B	27	M	C3D	208.2	314.6	267.5	-47.1
10	571062B	38	M	C8A	187.8	215.2	197.0	-18.2
11	566582B	28	M	C5A	206.3	259.0	229.3	-29.7
12	621696B	23	M	C5B	215.6	242.1	230.3	-11.8
13	630591B	37	F	C5A	184.8	151.7	131.2	-20.5
14	630661B	35	M	C5B	195.5	225.0	230.8	+5.8
15	646231B	21	M	T10A	219.3	211.6	187.3	-24.3
16	657381B	40	M	T10A	184.0	201.7	185.0	-16.7
17	048722B	25	M	T5A	211.9	211.4	172.0	-39.4
18	693776B	23	M	T11B	215.6	212.1	194.6	-17.5
19	699170B	35	M	C5A	195.5	208.0	198.6	-9.4
20	732346B	32	M	L1B	199.0	208.4	200.1	-8.3